Notice of Allowability	Application No. 09/767,215	Applicant(s) BERTIN, JOHN	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *interviews of 12/15/04, 02/15/05*.

2. ☒ The allowed claim(s) is/are *1-2, 21, 25-32, 34, 37-40, renumbered as 1-16*.

3. ☒ The drawings filed on 06/15/01 are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *12/15/04;02/15/05* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

It is noted that Applicant's response filed 01/30/04 placed the application in condition for allowance based on the record at that time. The Examiner s Amendment is made in lieu of reopening prosecution in order to remedy informalities which were brought to Applicant s attention for the first time in the telephone Interviews of 12/06/04, 12/15/04 and 02/15/05. Accordingly, no further extension of time is required to make the Examiner's Amendment which places the Application fully in condition for allowance.

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with JACK BRENNAN on 12/15/04, and 02/15/05.

The application has been amended as follows:

In the specification.

Replace the paragraph beginning at page 7, line 1 with the following amended paragraph:

The invention features a nucleic acid molecule which is at least 45% (or 55%, 65%, 75%, 85%, 95%, or 98%) identical to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the nucleotide sequence of the cDNA insert of the plasmid deposited with~~

~~the ATCC as Accession Number _____ (the "cDNA of ATCC _____"),~~ or a complement thereof.

Replace the paragraph beginning at page 7, line 6 with the following amended paragraph:

The invention features a nucleic acid molecule which includes a fragment of at least 150 (300, 325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, or 3900) nucleotides of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the nucleotide sequence of the cDNA of ATCC _____~~, or a complement thereof.

Replace the paragraph beginning at page 7, line 11 with the following amended paragraph:

In an embodiment, a CARD-14 nucleic acid molecule has the nucleotide sequence shown in SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the nucleotide sequence of the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 7, line 14 with the following amended paragraph:

Also within the invention is a nucleic acid molecule which encodes a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:2 ~~or the polypeptide encoded by the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 7, line 17 with the following amended paragraph:

The invention includes a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of SEQ ID NO:1, or SEQ ID NO:3~~, or the cDNA of ATCC _____ under stringent conditions~~.

Replace the paragraph beginning at page 7, line 34 with the following amended paragraph:

Also within the invention are: an isolated CARD-14 protein having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:2~~, or the amino acid sequence encoded by the cDNA of ATCC _____~~; an isolated CARD-14 protein having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to the CARD domain of SEQ ID NO:2 (e.g., about amino acid residues 10-116 of SEQ ID NO:2); an isolated CARD-14 protein having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to the coiled-coil domain of SEQ ID NO:2 (e.g., about amino acid residues 126-420 of SEQ ID NO:2); an isolated CARD-14 protein having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to the PDZ domain of SEQ ID NO:2 (e.g., about amino acid residues 568-660 of SEQ ID NO:2); an isolated CARD-14 protein having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to the SH3 domain of SEQ ID NO:2 (e.g., about amino acid residues 676-745 of SEQ ID NO:2); and an isolated CARD-14 protein having an amino acid sequence that is at least

about 65%, preferably 75%, 85%, 95%, or 98% identical to the guanylate kinase (GUK) domain of SEQ ID NO:2 (e.g., about amino acid residues 826-1004 of SEQ ID NO:2).

Replace the paragraph beginning at page 8, line 15 with the following amended paragraph:

Also within the invention are: an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 65%, preferably 75%, 85%, or 95% identical to SEQ ID NO:1~~,~~ or SEQ ID NO:3 ~~or the cDNA of ATCC _____~~; an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the CARD domain encoding portion of SEQ ID NO:1; an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the coiled-coil domain encoding portion of SEQ ID NO:1; an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the PDZ domain encoding portion of SEQ ID NO:1; an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the SH3 domain encoding portion of SEQ ID NO:1; an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 65% preferably 75%, 85%, or 95% identical to the guanylate kinase (GUK) domain encoding portion of SEQ ID NO:1; and an isolated CARD-14 protein which is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent

hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1 ~~or the noncoding strand of the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 9, line 4 with the following amended paragraph:

Another embodiment of the invention features CARD-14 nucleic acid molecules which specifically detect CARD-14 nucleic acid molecules, relative to nucleic acid molecules encoding other members of the CARD superfamily. For example, in one embodiment, a CARD-14 nucleic acid molecule hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or a complement thereof. In another embodiment, the CARD-14 nucleic acid molecule is at least 300 (350, 400, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, or 3900) nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or a complement thereof. In another embodiment, an isolated CARD-14 nucleic acid molecule comprises the CARD domain encoding portion of SEQ ID NO:1 or a complement thereof. In yet another embodiment, the invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a CARD-14 nucleic acid.

Delete the paragraph beginning at page 24, line 29, which paragraph begins with "A plasmid containing ....."

Replace the paragraph beginning at page 29, line 3 with the following amended paragraph:

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____,~~ or a complement of any of these nucleotide sequences, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequences of SEQ ID NO:1, or SEQ ID NO:3, ~~or the cDNA of ATCC _____ as a hybridization probe,~~ CARD-14 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., eds., Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Replace the paragraph beginning at page 29, line 19 with the following amended paragraph:

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____,~~ or a portion thereof. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Replace the paragraph beginning at page 29, line 25 with the following amended paragraph:

Moreover, the nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding CARD-14, for example, a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of CARD-14. The nucleotide sequence determined from the cloning of the CARD-14 gene allows for the generation of probes and primers designed for use in identifying and/or cloning CARD-14 homologues in other cell types, e.g., from other tissues, as well as CARD-14 homologues and orthologs from other mammals. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive nucleotides of the sense or antisense sequence of SEQ ID NO:1, SEQ ID NO:3, ~~the cDNA of ATCC _____~~, or of a naturally occurring mutant of one of SEQ ID NO:1, or SEQ ID NO:3, ~~or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 30, line 12 with the following amended paragraph:

A nucleic acid fragment encoding a "biologically active portion" of CARD-14 can be prepared by isolating a portion of SEQ ID NO:1, or SEQ ID NO:3, ~~or the cDNA of ATCC _____~~, which encodes a polypeptide having a CARD-14 biological activity, expressing the encoded portion of CARD-14 protein (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of CARD-14. For example, a nucleic acid fragment encoding a biologically active portion of CARD-14 includes a CARD domain.

Replace the paragraph beginning at page 30, line 19 with the following amended paragraph:

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence of SEQ ID NO:1, or SEQ ID NO:3, ~~and the cDNA of ATCC _____~~, due to degeneracy of the genetic code and thus encode the same CARD-14 protein as that encoded by the nucleotide sequence shown in SEQ ID NO:1, or SEQ ID NO:3, ~~or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 30, line 24 with the following amended paragraph:

In addition to the CARD-14 nucleotide sequence shown in SEQ ID NO:1, and SEQ ID NO:3, ~~and the cDNA of ATCC _____~~, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of CARD-14 may exist within a population (e.g., the human population). Such genetic polymorphism in the CARD-14 gene may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a CARD-14 protein, preferably a mammalian CARD-14 protein. Such natural allelic variations can typically result in 15% variance in the nucleotide sequence of the CARD-14 gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in CARD-14 that are the result of natural allelic variation and that do not alter the functional activity of CARD-14 are intended to be within the scope of the invention. Thus, e.g., 1%, 2%, 3%, 4%, or 5% of the amino acids in CARD-14 (e.g., 1,

2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, or 55 amino acids) are replaced by another amino acid, preferably by conservative substitution.

Replace the paragraph beginning at page 31, line 6 with the following amended paragraph:

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 150 (300, 325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, or 3900) nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~, or the cDNA of ATCC _____~~.

Replace the paragraph beginning at page 31, line 25 with the following amended paragraph:

In addition to naturallyoccurring allelic variants of the CARD-14 sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequence of SEQ ID NO:1~~,~~ or SEQ ID NO:3, ~~or the cDNA of ATCC _____~~, thereby leading to changes in the amino acid sequence of the encoded protein without altering the functional ability of the protein. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "nonessential" amino acid residue is a residue that can be altered from the wildtype sequence of CARD-14 protein without altering the biological activity, whereas an "essential" amino acid residue is required for biological

activity. For example, amino acid residues that are conserved among the CARD-14, proteins of various species are predicted to be particularly unamenable to alteration.

Replace the paragraph beginning at page 32, line 8 with the following amended paragraph:

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding CARD-14 proteins that contain changes in amino acid residues that are not essential for activity. Such CARD-14 proteins differ in amino acid sequence from SEQ ID NO:2, and yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 45% identical, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:2. An isolated nucleic acid molecule encoding a CARD-14 protein having a sequence which differs from that of SEQ ID NO:1, or SEQ ID NO:3 ~~or cDNA of ATCC _____~~, can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of CARD-14 (SEQ ID NO:1, or SEQ ID NO:3 ~~or the cDNA of ATCC _____~~) such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted nonessential amino acid residues. Thus, for example, 1%, 2%, 3%, 5%, or 10% of the amino acids can be replaced by conservative substitution. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain.

Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), betabranched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in CARD-14 is preferably replaced with another amino acid residue from the same side chain family. Alternatively, mutations can be introduced randomly along all or part of a CARD-14 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for CARD-14 biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

Replace the paragraph beginning at page 58, line 27 with the following amended paragraph:

A transgenic animal of the invention can be created by introducing CARD-14encoding nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The CARD-14 cDNA sequence, e.g., that of SEQ ID NO:1~~,~~ or SEQ ID NO:3~~ or the cDNA of ATCC ____~~ can be introduced as a transgene into the genome of a nonhuman animal. Alternatively, a nonhuman homolog or ortholog of the human

CARD-14 gene, such as a mouse CARD-14 gene, can be isolated based on hybridization to the human CARD-14 cDNA and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the CARD-14 transgene to direct expression of CARD-14 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the CARD-14 transgene in its genome and/or expression of CARD-14 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding CARD-14 can further be bred to other transgenic animals carrying other transgenes.

In the claims.

Claim 21 was amended as follows:

Claim 21. (Amended) An isolated polypeptide ~~comprising~~ consisting of a fragment of the amino acid sequence of SEQ ID NO:2, wherein said fragment comprises amino acids 10-116 of SEQ ID NO:2.

Claim 25 was amended as follows:

Claim 25. (Amended) An isolated polypeptide ~~comprising~~ consisting of a fragment of the amino acid sequence of SEQ ID NO:2, wherein said fragment comprises amino acids 826-1004 of SEQ ID NO:2.

Claim 32 was amended as follows:

Claim 32. (amended) ~~A fusion protein comprising the~~ The polypeptide of claim 1 linked by a peptide bond to a heterologous polypeptide.

Claim 34 was amended as follows:

Claim 34. (amended) ~~A fusion protein comprising the~~ The polypeptide of claim 21 linked by a peptide bond to a heterologous polypeptide.

Claim 37 was amended as follows:

Claim 37. (amended) ~~A fusion protein comprising the~~ The polypeptide of claim 25 linked by a peptide bond to a heterologous polypeptide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

February 15, 2005

SUSAN UNGAR, PH.D
PRIMARY EXAMINER